REMARKS

The Office action mailed 29 March 2007, has been received and its contents carefully noted. Claims 29-36 and 39 were pending, claims 31-34 and 36 were withdrawn from consideration, and claims 29, 30, 35 and 39 were rejected. Reconsideration is respectfully requested.

Rejection under 35 U.S.C. 102(b)

The Examiner rejected claims 29 and 35 under 35 U.S.C. 102(b) as being anticipated by Doretti et al. Specifically, the Examiner deemed that Doretti et al. teaches that AChE and BChE are widely used to monitor enzyme activity in the presence of inhibitors and that Doretti et al. discloses the use of linear relationships, which the Examiner interprets as being the same as the claimed "sensitivity coefficients".

Applicants respectfully submit that the present invention is directed to a device which is capable of assaying the activity or concentration of a single type of protein belonging to a family of similar proteins (exhibit biological/chemical properties which may react with a similar class of biomolecules/compounds, e.g. enzymes) in *a test sample which comprises the protein itself plus at least one similar protein.* The methods and devices of Doretti et al. are incapable of assaying a protein in a sample having other proteins with similar or overlapping activities.

Doretti et al. does disclose measuring the activity of substrates using proteins immobilized on a biosensor. However, in all the methods provided, Doretti et al. simply demonstrates that co-immobilized proteins (enzymes) on an amperometric sensor display an increase in response with increasing concentrations of substrates. Doretti et al. does not teach or suggest measuring the activity or concentration of a protein rather than its substrate.

In the methods and devices of Doretti et al. one *could* measure the concentration of a single desired protein such as AChE in a sample with an immobilized oxidative coupling protein such as choline oxidase *provided that no other proteins which have similar or overlapping activities (such as BChE) are present in the sample.* If, however, other proteins which have similar or overlapping activities are present in the sample, the methods and devices of Doretti et al. can not be used to measure the concentration or activity of only the single desired protein. The reason why the methods and devices of Doretti et al. can not assay the single desired protein

in the presence of a similar protein is that the similar protein contributes to the overall signal and without additional information it is impossible to dissect out the precise contribution of the similar protein to calculate the signal from the desired protein. In other words, there are at least two unknowns in the sample which produce a single observable signal.

In order to overcome this problem of proteins having similar or overlapping activities, the prior art methods usually purify or fractionate a sample in order to remove any similar proteins from the desired protein before assaying. For example, in a blood sample, AChE is bound to red blood cells and the serum or plasma contains the soluble BChE. In order to assay AChE or BChE, the blood sample is first fractionated by centrifugation in order separate the red blood cells from the serum or plasma. Then the AChE can be assayed from the red blood cell fraction and the BChE can be assayed from the serum or plasma. Unfortunately, prior art methods like this may detrimentally alter the assay results due to Le Châtelier's principle. Specifically, the equilibrium of a chemical system will shift in order to minimize a change in concentration, temperature, volume, pressure, or the like, and the shift in the equilibrium may substantially alter the activity of a given protein.

The present invention solves the problems of the prior art by adding additional substrates to the assay mixture such that the total number of the added substrates equals or exceeds the total number of proteins in the sample that have similar or overlapping activities (which would contribute to the overall signal if assayed according Doretti et al.). The reaction rates between each protein and each substrate is measured and the activity or concentration of the protein is determined from its sensitivity coefficient.

The sensitivity coefficient is not the same as the linear responses provided in Doretti et al.* Applicants respectfully direct the Examiner's attention to the response of 22 November 2006, the Specification and the prosecution of the granted parent patent, U.S. Patent No. 6,746,850. As claimed in the present invention, a sensitivity coefficient of a protein is calculated using inhibited dilutions and uninhibited dilutions of the protein. No where does Doretti et al. teach or suggest determining the reaction rates of inhibited and uninhibited dilutions. In fact, no

* In Doretti et al. the "sensitivity" obtained from the linear relationship is to the substrate, i.e. the protein is constant and the substrate was varied (and presented in a linear fashion). Doretti's "sensitivity" is to the level of detection of the substrate, whereas in the present invention, the "sensitivity coefficients" describe the activity of a protein to a fixed substrate concentration in the presence and absence of an inhibitor. Just because linear relationships are used does not mean they are the same.

where does Doretti et al. use any inhibitor of the cholinesterases such as an organophosphate, pesticide, or the like. Doretti et al. only shows the linear response to substrate (acetylthiocholine or butyrylthiocholine) concentration. See Figure 1 and Figure 3. Doretti et al. does not show any response to different enzyme (protein) concentration and NO inhibition curves using a cholinesterase inhibitor are taught or suggested. Thus, the linear relationships of Doretti et al. are clearly not the same as or equivalent to the claimed sensitivity coefficients.

Since Doretti et al. does not teach or suggest the claimed sensitivity coefficients, Doretti et al. does not teach or suggest the claimed means for determining the activity or concentration of a protein using its sensitivity coefficient for a substrate. Therefore, the rejection under 35 U.S.C. 102(b) should properly be withdrawn.

Rejection under 35 U.S.C. 103(a)

The Examiner rejected claims 29, 30, 35 and 39 under 35 U.S.C. 103(a) as being unpatentable over Doretti et al. in view of Magnotti et al. and further in view of Ellman et al. Specifically, the Examiner deemed that it would have been obvious to develop a handheld device with a biosensor to detect enzyme activity with all the requisite reagents for assays in the field. The Examiner asserted that the Test-Mate OP system has all the components required for the detection of cholinesterase as described by Ellman et al.

Applicants respectfully submit that Magnotti et al. and Ellman et al. do not alleviate the deficiencies of Doretti et al. Specifically, none of the cited references, alone or in combination, teach or suggest a means for determining the activity or concentration of a protein using its sensitivity coefficient for a substrate, wherein the sensitivity coefficient of a protein is calculated using inhibited dilutions and uninhibited dilutions of the protein. Each one of the methods and devices described by Doretti et al., Magnotti et al. and Ellman et al. require that the activity or concentration of a single type of protein be assayed in a serial manner from a sample that does not contain other proteins which exhibit similar or overlapping properties. No where do the cited references teach or suggest that one can assay a protein in the presence of other proteins having similar or overlapping properties by using its sensitivity coefficient. Thus, no where do the cited references teach or suggest the means for determining the activity or concentration of a protein using its sensitivity coefficient for a substrate as claimed.

In fact, Applicants respectfully submit that a prima facie case of obviousness has not been established as the cited references, alone or in combination, do not result in a means for determining the activity or concentration of a protein using its sensitivity coefficient for a substrate, wherein the sensitivity coefficient of a protein is calculated using inhibited dilutions and uninhibited dilutions of the protein.

Further, Applicants respectfully submit that the Test-Mate OP system is not capable of determining the activity or concentration of a protein using its sensitivity coefficient for a substrate, wherein the sensitivity coefficient of a protein is calculated using inhibited dilutions and uninhibited dilutions of the protein. Specifically, use of the commercially available system in accordance with the methods of the present invention requires that a plurality of substrates be used in each assay for each sample to determine the activity of one protein in the presence of other proteins having similar or overlapping properties. Since the Test-Mate OP system does not have the hardware for handling a plurality of substrates and the means to measure the reaction rates between each protein and each substrate from one assay sample, separate samples, incubation, and analysis are required.

Without major modifications to both its hardware and software, the Test-Mate OP system is not capable of assaying a protein in the presence of other proteins having similar or overlapping activities according to the present invention. In particular, the Test-Mate OP system would have to be modified to contain multiple channels to measure the response of a sample to a set of substrates and software which would calculate the concentration of a protein based on two or more equations (rather than its single linear equation) using its sensitivity coefficients in order to assay a protein in the presence of other proteins having similar or overlapping activities. Since the cited references do not teach or suggest using the claimed sensitivity coefficients and that the claimed sensitivity coefficients can be used to calculate the concentration or activity of a protein in a sample having similar or overlapping activities in accordance with the present invention, one skilled in the art would not be motivated to modify the Test-Mate OP system to provide means for determining the activity or concentration of a protein using its sensitivity coefficient.

Therefore, Applicants respectfully submit that the claimed invention is unobvious and the rejection under 35 U.S.C. 103(a) should properly be withdrawn.

Request for Rejoinder

Applicants respectfully request rejoinder of the withdrawn claims which ultimately depend on claim 29.

Request for Interview

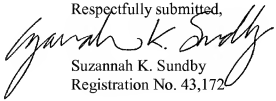
Either a telephonic or an in-person interview is respectfully requested should there be any remaining issues.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Therefore, it is respectfully requested that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

It is not believed that extensions of time are required, beyond those that may otherwise be provided for in accompanying documents. However, in the event that additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. 1.136(a), and any fees required therefor are hereby authorized to be charged to **Deposit Account No. 210-380**, Attorney Docket No. **034047.003DIV1 (WRAIR 00-23)**.

Respectfully submitted,



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